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| EXAMINER |
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| ART UNIT | PAPER NUMBER |
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**DATE MAILED:** 05/07/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on the election of 3-3-97 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

**Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:**

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

**Part II SUMMARY OF ACTION**

1. ☒ Claims 1-21 are pending in the application.
   Of the above, claims 1-11 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 12-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-21 were are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

**EXAMINER'S ACTION**

1. Applicant's election of Group II, claims 12-21 in Paper No. 11 of 3-3-97 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

A new title that is more specific to the elected invention is suggested, such as: "GENE ENCODING TNF INHIBITOR AND METHOD OF PRODUCTION"

3. Claims 12-16, 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-16 are vague and indefinite in the use of "**capable** of directing...." and "**capable** of being transferred". Here the issue is the use of "**capable**". While such a term is not indefinite in a general sense and across the board in patent law, it does render the claims indefinite if its meaning and context as used in the claims is not clear. As used herein, it is not clear and possibly non-enabling (as will be set forth hereinbelow) if the DNA within the meaning of the claim has the ability to direct the host cell to produce such a protein when the specifics of the DNA or, the protein have not be sufficiently identified.

Claims 12-16 are indefinite and incomplete, and non-enabling for failing to recite sufficient process limitations. The preamble of the claims refers to a methods of producing a TNF inhibitor, however, none of these claims recite a recovery of isolation/purification step. In order to meet this preamble limitation and clearly show that the TNF inhibitor is produced one must necessarily recover it. Therefore, applicants should amend the claims to refer to a "recovery step" or to a specific isolation/purification.

Claims 15-16 and 20-21 are indefinite and confusing in the use of "Δ51" "Δ53" because the use of the "Δ" symbol here is confusing, and it is not clear if applicants intend that the amino

acid at this position is deleted. These symbols, to presumably represent modified/mutated forms of the TNF inhibitor, are first mention at page 4 of the specification, but a specific definition for what applicant intend by this was not provided. Definitions should be provided at the first appearance of the term/phrase/symbol used-especially if this is not a well known and art recognized meaning, or if there are multiple meaning for the symbol (as is the case herein). This symbol is again reference at page 14 and is referred to for Examples 17 and 22 , but these page, nor does any other place in the specification appear to provide a clear and concise meaning for what it intended. It is not clear if applicants intend for this to mean the deletion of just residues 51 or 53, or if this represent N-terminal deletions of the first 51 or 53 amino acids, or if this is intended or represent C-terminal deletions of the last 51 or 53 residues. Clarification/correction is requested or the claims should be amended to refer to a deleted product.

4. Claims 12-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids that encode for the full length, precursor forms and certain specific mutants of the 30kD and 40kD TNF inhibitor; and for the recombinant production of such, does not reasonably provide enablement for: a) any TNF inhibitor of unspecified characteristics, and the production of such, as in claims 17 and 12 respectively; b) any TNF inhibitor of limited and insufficient characteristics, and the production of such, as in claims 18-21 and 13-16 respectively [Note: claims 15-16 and 20-21 are included in this part of the rejection because the merely recite and broad name, a limited MW and presumably a point mutation].

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The various aspects to this scope rejection as set out above which will be discussed individually hereinbelow. First of all, as stated above, claims 12-16 are incomplete and none enabling for the recombinant production of the TNF inhibitor because in order to ensure its production/preparation, there must be a recovery/isolation step, thus the claims should be amended to recite such.

The specification is not commensurate in scope with the breadth of the claims for any TNF inhibitor of unspecified characteristics. The use of a name and/or abbreviation, absent any distinguishing characteristics or defining features, does not serve to enable the skilled artisan of how to make and use all those proteins or others products that can act as inhibitors of TNF based on the limited teachings in the specification. Applicants have only provided enablement for the 30 and 40kD TNF inhibitory protein that have a specific make-up/amino acid sequence, but this claims broadly encompasses compounds or other biological products that will inhibit the activity of TNF. Exemplary of such are the known proteinaceous molecules that will inhibit the activity of TNF as well as IL-1. The enablement for the 30 and/or 40 kD TNF inhibitors of Figures 19 or 38 would not be predictive of any and all other inhibitors of TNF, because there are physical, structural, and functional differences between products that can posses this activity such that one would not be expected to function in the same manner and be predictive of another product that would possess the desired activity. For example, certain mutants or antagonist for the protein or for its corresponding ligand may act to inhibit the activity of the claimed protein, but these products would display their function in a different manner; and this is also true for antibodies. The fact that one would have an assay that would be able to measure the inhibitory activity of the claimed proteins, does not reasonably assure the skilled artisan that this assay would be usable and successfully predictable for any and all compounds. The skilled artisan would encounter undue experimentation and a substantial amount of trail and error for picking and choosing the appropriate agents/compounds/proteins to test, and would further expend a lot of time in testings the various agents and selecting them for applicants intended use. While the method claims (12-16) appear to recite several steps, these are very generic and non-specific step that would be applicable to many protein, because these claim, especially claim 12 fails to recite any identifying characteristic of the protein to be produced, and the step are too generic to ensure that the skilled artisan would be able to obtain a TNF inhibitory protein following these recited steps. Even though claims 13- 16 recite a MW for the protein to be produced, this still constitute limited

characterization, and would be subject to the same kind of problems as discussed above for claim 12 and 17.

Claims 15-16 and 20-21 would appear to represent some kind of modified/mutated form of the TNF inhibitor, but as discussed above, the exact nature of what applicants intend has not been made clear. Therefore, as written, the claims do not appear to be enabling from the teachings of the specification. Applicants have not provided teachings, evidence or guidance for the specific residues that can be deleted with assurance that they will maintain the desired activity. The skilled artisan would again be faced with undue experimentation and trail and error in trying to determine the appropriate residue that can be deleted and still product a protein that possess the proper 3-dimensional structure; proper folding patterns; and the desired function. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino substitutions and deletions are generally possible in any given protein, these deletions generally occur for a limited number of amino acids at the N or C-terminals, or at one or two residue positions within the protein's sequence. Certain positions in the sequence are critical to the protein's structural/ functional relationship, e.g. such as various sites or regions where the biological activity resides or regions directly involved in binding, stability, or catalysis; and in providing the correct three-dimensional spatial orientation for biologically active or binding sites, or for sites which represent other characteristics/properties of the protein. These or other regions may also be critical determinants of antigenicity. These various regions can tolerate only relatively conservative substitutions or no substitutions and limited deletions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant such vast deletion if a total of either 51 or 53 residues are to be deleted from the protein. Therefore Applicant has not presented enablement commensurate in scope with the claims. Based on all of the above

discussion, the claims are only enabling for their full scope. In a similar manner, claims 15-16 and 20-21 could represent "fragments" of the 30kD and 40KD TNF inhibitor. What portion or fragment region, or residue this should represent has not been taught; nor is it clear how long the portion or fragment has to be and it should cover any biologically significant region.. Without such information, the skilled artisan would have to resort to trial-and-error and be faced with undue experimentation for making and using peptides for any part of the TNF inhibitors.

5. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 12-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14, 17-19, 27-29 and 31-35 of copending Application No. 08/092538. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope and appear to be directed to N.A. that encode the same TNF inhibitors-despite slight difference in the wording or in the manner in which certain characteristics are recited in the claims. The method of production of the protein appears to only differ in the recitation of the number of generic steps, and are thus not patentable one over the other, because they would be obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-21 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Wallach.

The prior art discloses DNA sequences that will encode for a protein, although referred to by a different name, that is considered a binding protein for TNF; as well as the recombinant production of such (see the claims and examples).. The protein has the same N-terminal sequence as that of the instant protein. Based on such, the protein reasonably appears to be the some despite the fact that the entire amino acid sequence is not disclosed as is with some of the instant claims. However, the amino acid sequence is inherent to a protein, and to further characterize a prior art protein product by disclaiming other characterizing features, such as the amino acid sequence does not impact patentability to the prior art protein. Accordingly the burdens is upon applicants to prove a patentable difference (In re Best, 195 USPQ 430 and In re Swinehart, 169 USPQ 226 , and Ex parte Gray 10 USPQ 2d. 1922). In view of the confusion with regard to the meaning and intent of "Δ" form of the protein, these claims are included in this rejection, and because the prior art briefly discuss modified forms of the protein, these claims would have been prima facie obvious from such.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The other are is cited as of interest to show related art.

8. Any inquiry concerning this communication should be directed to G D. Draper at telephone number (703) 308-4232.

GARNETTE D. DRAPER
PRIMARY EXAMINER
GROUP 1800